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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
Masahiko DOHI, et al.
Serial No.: 09/125,814
Field: August 26, 1998
For: POWDERY COMPOSITION FOR NASAL ADMINISTRATION

Group Art Unit : 1615
Examiner : Alysia Berman

DECLARATION UNDER 37 C.F. 1.132

Hon. Commissioner of Patents and Trademarks,
Washington, D.C. 20231

Sir:

I, Masahiko Dohi, c/o TEIJIN LIMITED, DDS Laboratories, 4-3-2 Asahigaoka, Hino, Tokyo191-8512, Japan, do hereby declare:

That I am by profession a research scientist having earned a Master's degree in pharmaceutics from Science University of Tokyo in March 1990;

That I have been employed by TEIJIN LIMITED, Tokyo, Japan, since March 1990;

That I have been engaged in research into the development of pharmaceutical products in the same company to date;

That I am a co-inventor of the invention disclosed in the above-identified U.S. application (hereinafter referred to as "present invention" for brevity) and hence I am fully familiar therewith;

That I have read and am fully familiar with the art cited against claims of the above-identified U.S. application (hereinafter referred to as "present application" for brevity);

That I personally conducted or supervised the conduct of all of the work reported in the examples including the comparative example in the specification of the present application, and the results obtained are as set forth therein;

That , to show that the present invention should be nonobvious from cited prior art, I carried out the following explanations.

I would like to explain detailedly the Attachment B we submitted on Jan. 12, 2000.(at the interview)

Before my explanation, I would like to correct the number in the figure in 4) as following; the highest plasma profile resulted in by 3) not 1), middle plasma profiles resulted in by 1) not 2), and the lower plasma profile resulted in by 2) not 3).

Firstly I'd like to explain the powder conditions illustrated in 1), 2), 3-a) and 3-b) of the attachment B.

The illustration in 1) shows powder manufactured by ordinary mixing with Microcrystalline cellulose (MCC) showing water-absorbing and water-insoluble property, Hydroxypropylcellulose (HPC) showing water-absorbing and gel-forming property, and an active ingredient simultaneously. In this case the active ingredient was distributed homogeneously in the powder preparation and the active ingredient adhered to MCC and HPC with their volume ratio in the formulation. However, the amount of the active ingredient adhered to the bases is less than those by other powders shown in 2), 3-a) and 3-b). Because ordinary mixing doesn't have enough press-on force to adhere powder to powder. We manufactured powder preparation by ordinary mixing; 5 mg of carboxy fluorescein (CF) as an ingredient, 400 mg of MCC and 100 mg of HPC were simultaneously mixed in a glass bottle on a ball-mill by rotating the mill. The condition of the powder is shown in Fig.3. The Fig.3 shows that little active ingredient adhere to bases; most of base shows white derived from their own color; that means little active ingredient adhered to bases. If the active ingredient adhere to bases, they could be stained yellow because of yellowish color of CF.

Also the illustration in 2) shows powder manufactured by Suzuki's method, Ex.1(b) in U.S. 4,613,500; that is at first 5 mg of CF and 100 mg of HPC dissolved in 10 mL of 5 mM NaCl aqueous, and resulting solution was lyophilized and sieved at 38-150 micrometer, and then mixed with 400 mg of MCC. In the lyophilization step, most of CF adhered to HPC. Consequently most of CF also adhered to HPC in the formulation. It could be explained by Fig.6; MCC shows white derived from itself. On the other hand, HPC does yellow as it was stained by CF.

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Here please compare yellow concentration between Fig. 6 and 5. Regarding these two powder preparations the volume ratio of MCC and HPC is same, MCC/HPC = 4/1 and CF content is also same. Since most of CF adhered to MCC in Fig. 5 and most of CF adhered to HPC in Fig. 6, it is reasonable that Fig.6 shows deeper yellow than Fig.5 does.

Figs.3, 5, and 6 were taken with a video microscope (VMS-5000, SCALAR Co., Tokyo, Japan) and a color video printer (UP-1800, SONY Co., Tokyo, Japan) at magnification 41 or 205×.

In the case of 3-b) I cannot submit picture which shows this condition. However adhering between particles is influenced on their size. I speculate from the physicochemical aspect that particles which have different particle size mutually adhere easier than those have same size particle do. In the case of nasal powder, most of ingredient have less than 10 micro meter. The active ingredient adhere easier to MCC (38-150 micro meters) than to HPC, if the particle size of HPC reduces compared to MCC.

Secondly I would like to explain plasma profiles by these powders.
Please see Fig.4. In this figure M/H powder 3, M/H powder 2, and M/H powder 4 means powders shown in 3-a), 1) and 2) of Attachment B, respectively.
Apparently 1) and 2) shows less absorption than 3-a).

With regard to powder shown in 3-b), I submit other data; effect of HPC particle size in MCC/HPC mixture. These data were disclosed at 5th US-Japan symposium on DDS in Maui last year. The powders, composed of MCC whose size is 38-150 micrometers, several size of HPC whose size are 38-63, 63-90, 90-150 and 150-350 micrometers, and FITC labeled dextran (FD-4) whose molecular weight is 4,400 dalton as one of active ingredient, were administered into rabbits (see Fig.1). These powders were manufactured by firstly mixed with MCC and FD-4 and then mixed with HPC. Fig.2

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I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 21 day of February 2000

Masahiko Dohi

Masahiko Dohi

Encl.

(1) Attachment B
(2) Fig.1
(3) Fig.2
(4) Fig.3
(5) Fig.4
(6) Fig.5
(7) Fig.6

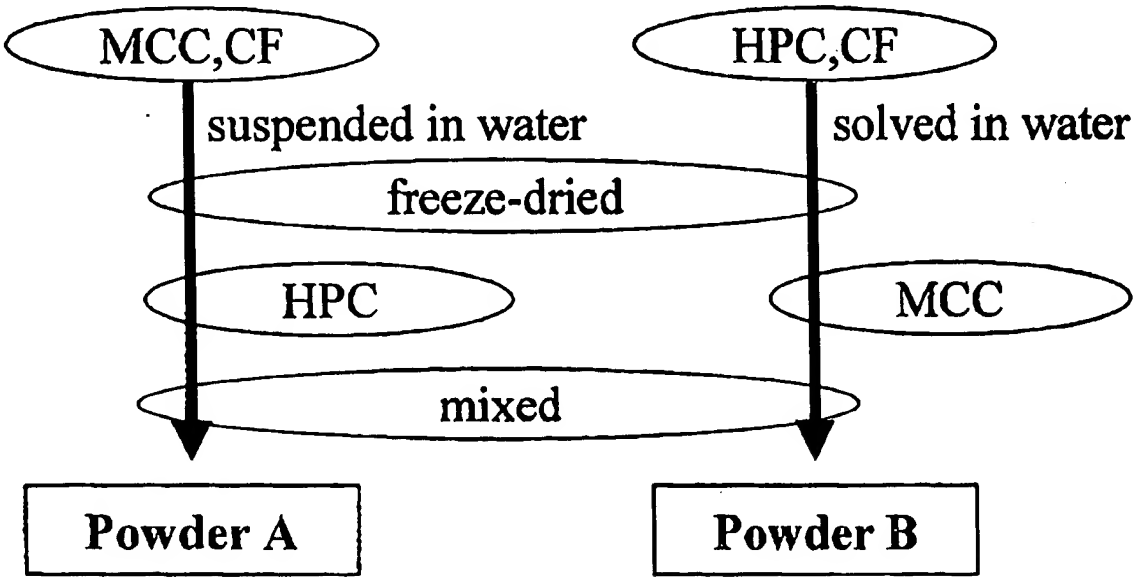
Fig. 1

Design of formulation

1 distribution of active ingredients in the MCC/HPC mixture;

<Study> Powder A (CF distributed mainly on MCC) and powder B (on HPC) were manufactured and dosed into rabbits.

Scheme of manufacturing



composition	
MCC	800
HPC	200
CF	1

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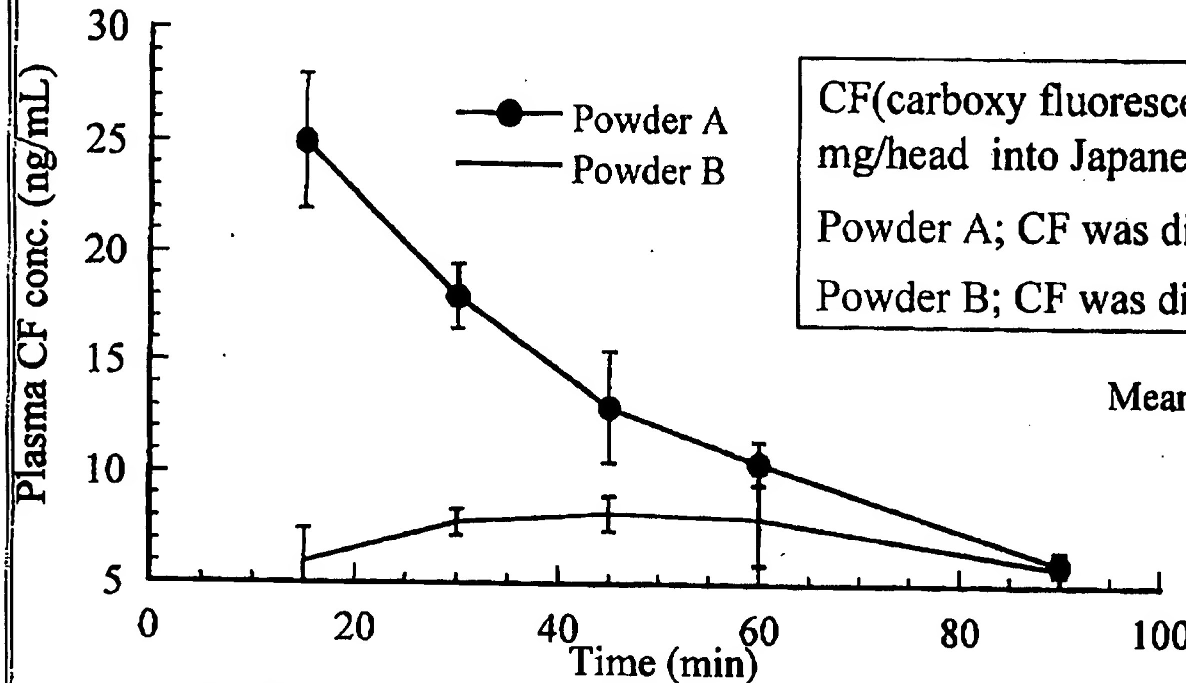
Fig. 2

Effect of CF distribution to base materials on plasma profiles



CF(carboxy fluorescein) was dosed at 0.1 mg/head into Japanese White rabbits.

Powder A; CF was distributed mainly on MCC.

Powder B; CF was distributed mainly on HPC.

Mean ± SD (n=3)

Distribution of CF in powder preparation played a critical role to attain high nasal absorption.

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